Improvement in Perioperative Outcome After Hepatic Resection

Analysis of 1,803 Consecutive Cases Over the Past Decade

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Objective

To assess the nature of changes in the field of hepatic resectional surgery and their impact on perioperative outcome.

Methods

Demographics, extent of resection, concomitant major procedures, operative and transfusion data, complications, and hospital stay were analyzed for 1,803 consecutive patients undergoing hepatic resection from December 1991 to September 2001 at Memorial Sloan-Kettering Cancer Center. Factors associated with morbidity and mortality and trends in operative and perioperative variables over the period of study were analyzed.

Results

Malignant disease was the most common diagnosis (1,642 patients, 91%); of these cases, metastatic colorectal cancer accounted for 62% (n = 1,021). Three hundred seventy-five resections (21%) were performed for primary hepatic or biliary cancers and 161 (9%) for benign disease. Anatomical resections were performed in 1,568 patients (87%) and included 544 extended hepatectomies, 483 hepatectomies, and 526 segmental resections. Sixty-two percent of patients had three or more segments resected, 42% had bilobar resections, and 37% had concomitant additional major procedures. The me- dian blood loss was 600 mL and 49% of patients were trans- fused at any time during the index admission. Median hospital stay was 8 days, morbidity was 45%, and operative mortality was 3.1%. Over the study period, there was a significant in- crease in the use of parenchymal-sparing segmental resec- tions and a decrease in the number of hepatic segments re- sected. In parallel with this, there was a significant decline in blood loss, the use of blood products, and hospital stay. De- spite an increase in concomitant major procedures, operative mortality decreased from approximately 4% in the first 5 years of the study to 1.3% in the last 2 years, with 0 operative deaths in the last 184 consecutive cases. On multivariate analysis, the number of hepatic segments resected and oper- ative blood loss were the only independent predictors of both perioperative morbidity and mortality.

Conclusions

Over the past decade, the use of parenchymal-sparing seg- mental resections has increased significantly. The number of hepatic segments resected and operative blood loss were the only predictors of both perioperative morbidity and mortality, and reductions in both are largely responsible for the de- crease in perioperative mortality, which has occurred despite an increase in concomitant major procedures.

Lortat-Jacob's report of a true anatomical right hepatec- tomy for cancer in 1952 ushered in the modern era of hepatic resectional surgery.[1] However, the subsequent ex- perience with hepatic resection was far from encouraging.

In 1977, Foster and Berman reported a multicenter analysis of 621 hepatic resections for a variety of indications.[2] In this study, operative mortality was 13% and over 20% for major resections (hepatectomy, extended hepatectomy), with 20% of the deaths resulting from hemorrhage.

Over the past decade, many large series have documented better perioperative results, with operative mortality rates typ- ically less than 5% in high-volume centers.[3–7] As a result, hepatic resection has evolved into the treatment of choice for selected patients with benign and malignant hepatobiliary dis- ease. Also, with improvement in the safety of hepatic resection, indications for its use have broadened, and partial hepatectomy

in combination with other major procedures is now performed with greater frequency.[8,9]

No single factor is responsible for the marked improvement in perioperative outcome. General improvement in operative and anesthetic technique, better patient selection, and the emergence of hepatobiliary surgery as a distinct area of specialization have all been cited, and probably all play a role.[8] A better understanding of hepatic anatomy and increasing application of anatomically based resections are perhaps the most important factors in this regard.

With this refined appreciation of hepatic segmental anatomy has come an awareness of the feasibility of segment-oriented resections. It has been established that, in the appropriate setting, parenchymal-sparing segmental resections offer the same benefit as classic lobar resections with less risk than is associated with removal of a large volume of functional liver tissue.[3,10,11] In addition, segmental resections are clearly superior to wedge resections with respect to blood loss and tumor clearance.[12]

The practice of hepatic resectional surgery thus continues to evolve, but few large, contemporary studies have specifically evaluated the impact of these changes.[8] The present study analyzes consecutive, unselected patients undergoing hepatic resection over the past decade to further define factors associated with morbidity and mortality and to evaluate trends in operative and perioperative variables over the period of study.

METHODS

The hepatobiliary patient database at Memorial Sloan-Kettering Cancer Center (MSKCC) was established in 1991, and all patients undergoing a partial hepatectomy since that time were identified and included in this analysis. Patients who underwent a liver wedge biopsy only were excluded.

Our general approach to patient evaluation and hepatic resection is described elsewhere.[13,14] All patients underwent a thorough history and physical examination. A formal cardiopulmonary evaluation was obtained in patients with comorbid medical conditions suggesting an increased operative risk and in all patients over age 65. A full radiologic extent of disease evaluation was performed on all patients, although the nature of the studies obtained varied depending on the diagnosis. Cases and radiographic studies were reviewed at a twice-weekly multidisciplinary disease management conference attended by surgeons, diagnostic and interventional radiologists, oncologists, and gastroenterologists, and additional studies were obtained as warranted. Patients undergoing operation were explored through an extended right subcostal incision or bilateral subcostal incision with vertical midline extension; a few patients required a thoracoabdominal incision. Since 1997, staging laparoscopy has been used with increasing frequency.[15,16] All patients underwent a full abdominal exploration with bimanual palpation of the liver and intraoperative ultra-

sound. For most resections, inflow vascular control was obtained before parenchymal transection, which was performed using a crushing technique and with an intermittent Pringle maneuver (porta hepatis clamp). Also, for major resections, hepatic venous outflow control was typically achieved extrahepatically before dividing the liver. Resections were performed with a low central venous pressure (<5 mmHg) and with patients in the Trendelenburg position. Abdominal drains were not used after most resections, except those that included a biliary resection and reconstruction or when there was persistent bile leakage from the cut surface of the liver.[17] Following operation, patients were not sent routinely to the intensive care unit but were monitored overnight in the recovery room and then transferred to the ward, provided they were stable clinically.

Preoperative variables analyzed included patient demographics, diagnoses, comorbid medical conditions, and laboratory values (bilirubin, albumin, creatinine, platelet count). Intraoperative data were obtained from the operative note and the anesthesia record and included operating time, portal triad clamp time (Pringle time), estimated blood loss (EBL), hepatic resections, and any other procedures performed.

The number of hepatic segments resected was determined from the procedure listed: extended hepatectomy, five segments; right hepatectomy (lobectomy), four segments; left hepatectomy (lobectomy), three segments; central hepatectomy, three segments; and left lateral segmentectomy, right anterior or posterior sectorectomy, two segments. Patients who underwent an enucleation were considered to have had zero segments resected, while those submitted to a wedge resection were considered to have had one segment resected. When multiple resections were performed, the number of segments resected represented the total for the entire procedure. A segmental resection was defined as any sublobar, anatomically based resection of one or more segments, either en bloc or as separate procedures. When multiple hepatic procedures were performed, the most extensive resection was considered the main procedure, with the others listed as additional hepatic procedures. Bilobar resections were defined as any procedure that involved resection of segments from both the left and right hemi-livers. A repeat resection was defined as any resection performed in a patient who had previously undergone a partial hepatectomy.

The performance of concomitant major procedures in addition to the principal hepatic resection constituted a "complex hepatectomy." Patients in this group included those who underwent one or more major extrahepatic procedures (organ resection, biliary resection/reconstruction or bile duct exploration, portal vein and/or vena cava resection/reconstruction, porta hepatis lymphadenectomy, thoracotomy) and/or those who underwent additional hepatic resectional or ablative procedures. Hepatic artery pump placement, cholecystectomy, colostomy/ileostomy reversal, and liver wedge biopsy were not considered additional

major procedures. Patients who underwent a single hepatic resectional procedure of any type, without any additional major procedures, were placed in the "hepatectomy only" group.

The postoperative variables analyzed included complications (any), hospital length of stay (LOS), intensive care unit (ICU) admission, and mortality. Operative mortality was defined as any death resulting from a complication of the operation, whenever it occurred. Transfusion of any blood products (packed red cells, whole blood, fresh-frozen plasma or platelets) during the operation or at any time during the hospital stay after operation was also recorded. Data regarding the resected specimen, including number of tumors, size of the largest tumor, and any hepatic parenchymal abnormalities, were obtained from the pathology record. For all specimens, sections of liver were taken from areas distant from the tumor, and underlying parenchymal abnormalities (e.g., steatosis, cirrhosis) were reported according to widely applied and accepted criteria.

The association of variables with mortality and complications was tested using the Fisher exact test for dichotomous covariates and the t test for continuous variables (using a logarithmic transformation as necessary). Stepwise logistic regression was used for multivariate models. Patients were divided into five groups based on the date of operation. Variables related to perioperative outcome were analyzed for each of the five groups, and trends over time were tested for significance using the Cochran-Armitage test.[18] Numerical data are expressed as the mean ± standard error unless otherwise indicated.

RESULTS

Demographics

From December 1991 to September 2001, 1,803 consecutive patients underwent a partial hepatectomy at MSKCC. There were 906 women and 879 men, and the average age was 58.6 ± 0.3 years (range 0.2–89) (Table 1). Seven hundred sixty-seven patients (43%) had at least one comorbid medical condition, most commonly hypertension (23%), cardiac disease (16%), and diabetes mellitus (8%). Preoperative laboratory abnormalities (based on the normal range at MSKCC) were common and included hyperbilirubinemia (>1 mg/dL) in 196 patients (11%), hypoalbuminemia (<4 g/dL) in 468 (26%), thrombocytopenia (<160,000/μL) in 189 (11%), and elevated serum creatinine (>1.3 mg/dL) in 112 (6%).

Diagnoses

One thousand six hundred forty-two patients (91%) had a malignant diagnosis, with metastatic liver disease present in 1,249 (69%) (Table 2). The most common diagnosis overall was metastatic colorectal cancer (n = 1,021), but there was a wide spectrum of other metastatic tumors resected. Pri-

Table 1. PATIENT DEMOGRAPHICS AND COMORBID CONDITIONS

Male/female	879/906
Age (years)	58.6 ± 0.3 (0.2–89)
Patients with ≥1 comorbid conditions	767 (43%)
Patients with ≥2 comorbid conditions	252 (14%)
Hypertension	411 (23%)
Cardiac disease	281 (16%)
Ischemic heart disease/cardiomyopathy (119)	
Dysrhythmia (96)	
Valve disease (66)	
Diabetes mellitus	152 (8%)
COPD/asthma	107 (6%)
Peripheral vascular disease	35 (2%)
Other[1]	93 (5%)
Patients with chronic hepatitis[2]	84 (5%)
Preoperative tests	n (%) Abnormal
Bilirubin	
>1 mg/dL	196 (11%)
>2 mg/dL	68 (4%)
>10 mg/dL	18 (1%)
Albumin	
<4 g/dL	468 (26%)
<3.5 g/dL	160 (9%)
Platelets	
<160,000/μL	189 (11%)
<100,000/μL	21 (1%)
Creatinine	
>1.3 mg/dL	112 (6%)

[1] Includes arthritis (27), history of DVT/PE (19), major depression (10), other endocrine disorders (9), chronic renal failure (8), parkinsonism (4), osteoporosis (4), tuberculosis (2), seizure disorder (2), Alzheimer's disease, Turner's syndrome, sarcoidosis, amyloidosis, systemic lupus erythematosus, multiple sclerosis, aplastic anemia, Lyme disease (1 each).

[2] Includes only those patients with positive serology for hepatitis B and C. Not all patients were routinely tested.

mary hepatic and biliary cancers accounted for 375 cases (21%), of which hepatocellular carcinoma was the most common (188 patients), followed by extrahepatic biliary malignancy (gallbladder carcinoma [77 patients] and hilar cholangiocarcinoma [65 patients]). One hundred sixty-one patients (9%) had benign hepatic or biliary disease, hemangioma being the most common (56 patients); 17 resections were performed for benign biliary strictures.

Hepatic Resections and Other Procedures

One thousand five hundred sixty-eight patients (87%) underwent anatomically based resections, which were predominantly extended right or left hepatectomy (trisegmentectomy, 544 patients, 30%) and right or left hepatectomy (lobectomy, 483 patients, 27%). Five hundred twenty-six patients (29%) underwent a segmental resection, consisting either of an en bloc resection of more than one segment or resection of multiple discontiguous segments (344) or a unisegmentectomy (182). There were 15 central hepatecto-

Table 2. PATIENT DIAGNOSES

Diagnoses	n (%)
Benign	161 (9%)
Hepatic	134
Hemangioma (56)	
FNH (22)	
Adenoma (17)	
Cystadenoma (8)	
Polycystic disease (8)	
Complex cysts (8)	
Hydatid disease (6)	
Other (10)[1]	
Biliary	27
Bile duct stricture (17)	
Choledochal cyst/Caroli's (3)	
Other (7)[2]	
Malignant	1,642 (91%)
Metastatic Disease	1,249
Colorectal (1,021)	
GU/GYN (73)[3]	
Neuroendocrine (51)	
Sarcoma (40)	
Breast (22)	
Melanoma (11)	
Non-colorectal GI (10)	
Other (21)[4]	
Primary Malignancy	375
Hepatic parenchymal (233)	
-HCC (188)	
-Peripheral cholangiocarcinoma (40)	
-Hepatoblastoma (5)	
Extrahepatic biliary (142)	
-Gallbladder cancer (77)	
-Hilar cholangiocarcinoma (65)	
Other[5]	18

[1] Abscess (4), fatty infiltration (3)*, regenerative nodule (2)*, solitary fibrous tumor.
[2] Cystadenoma (3), abscess (2)*, adenomyomatosis*, porcelain gallbladder*.
[3] Germ cell (22), adrenal (17), ovarian (16), renal cell (7), uterine (6), other (5).
[4] Lung (9), neuroblastoma (3), adenoid cystic carcinoma (2), thyroid (2), squamous cell carcinoma (2), histiocytoma, paraganglioma, thymoma.
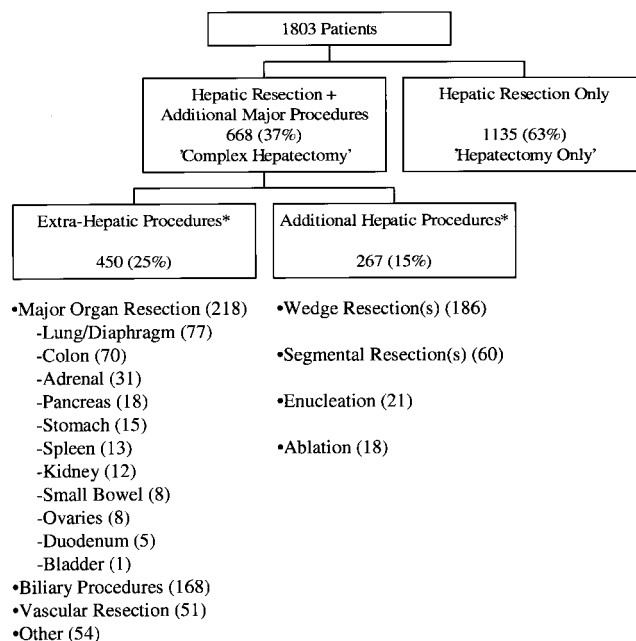[5] Sarcoma (direct extension [6], primary [3]), hemangioendothelioma (4), carcino-sarcoma, hemangiopericytoma, lymphoma (primary), neuroendocrine (primary), renal cell (direct extension).
* Unable to exclude malignancy.

Figure 1. Breakdown of operative procedures performed. Patients in the "hepatectomy only" group underwent a single hepatic resectional procedure with no additional major procedures. Patients in the "complex hepatectomy" group underwent the principal hepatic resection plus one or more additional major procedures. *49 patients underwent one or more extrahepatic procedures and one or more additional hepatic procedures.

mies. Nonanatomical wedge resections or enucleations were performed in 174 patients (10%) and 61 patients (3%), respectively.

The average number of hepatic segments resected was 3.3 ± 0.4 (range 0–6), and 1,113 patients (62%) underwent resection of three or more segments. Seven hundred forty-nine patients (42%) had bilateral resections, 85 (5%) had one or more repeat hepatic resections, and 118 (7%) underwent an en bloc or isolated caudate lobe (segment 1) resection.

In 1,135 patients (63%), a single hepatic resectional procedure was performed with no concomitant major procedures ("hepatectomy only" group), while 668 patients (37%) underwent the principal hepatic resection along with

one or more additional major procedures ("complex hepatectomy") (Fig. 1). The latter group was further divided into those who underwent one or more additional hepatic procedures (267 patients) (single or multiple wedge resections or segmental resections, enucleations, or ablations) or one or more extrahepatic procedures (450 patients). The most common extrahepatic procedure was a concomitant major organ resection (218 patients), followed by major biliary procedures (168; bile duct resection/reconstruction [155] or bile duct exploration [13]) and vascular resections (portal vein or vena cava resection/reconstruction [51]). Other extrahepatic procedures included lymphadenectomy (subhilar, retroperitoneal [38]), chest wall/abdominal wall reconstruction (8), thoracotomy (4), and resection of retroperitoneal tumor (4). Forty-nine patients underwent both an extrahepatic procedure and additional hepatic procedures. It should be noted that patients with hilar cholangiocarcinoma or gallbladder cancer routinely underwent a concomitant sub-hilar lymphadenectomy,[19] which was not coded as a second major procedure.

In 997 patients (55%), the non-tumor-bearing liver was histologically unremarkable. Of the remainder, the most common underlying hepatic parenchymal abnormalities were steatosis (325), cholestasis and/or inflammation (253), and cirrhosis/fibrosis (158). Seventy-nine patients had multiple abnormalities described. The liver histology was unavailable in 148 patients.

Perioperative Results: All Patients

The operative and perioperative results for all patients are summarized in Table 3. The median operating time was 4 hours, porta hepatis clamp time (Pringle) was 28 minutes, and EBL was 600 mL. There was a progressive increase in EBL as the number of segments resected increased ($P <$ .001). Eight hundred eighty patients required transfusion of blood products during or after operation, 15% of whom received only fresh-frozen plasma. Median LOS was 8 days, and 112 patients (6%) required ICU care. The perioperative morbidity was 45% (817 patients), with 345 patients (19%) experiencing multiple complications. Infections occurred in 41% of patients with complications. In total, there were 1,350 complications, the most common of which were liver and/or biliary-related (369), although pulmonary complications were nearly as common (344). The most common complication overall was an infected or sterile perihepatic fluid collection (207).

The operative mortality was 3.1% (55 patients), and there were no deaths in the last 184 consecutive cases. In the majority of cases, the cause of death was multifactorial, and a single underlying event was difficult to identify. Infections played a prominent role in the deaths of 23 patients (42%). Hepatic failure was observed in 19 patients but was apparently the sole cause of death in only 6 patients. More commonly, liver failure occurred within the context of systemic sepsis and/or multisystem organ failure (11 patients) or after major gastrointestinal hemorrhage (2 patients).

Perioperative Outcome: Extent of Operation

The number of hepatic segments resected had a profound impact on perioperative morbidity and mortality (Fig. 2). In patients who underwent a resection of zero or one segments, the complication rate was 32%; it increased progressively to 75% in patients who underwent resection of six segments ($P <$ .001). There was a similar trend in operative mortality, which increased from less than 1% in patients who underwent resection of less than three segments to 5% and 7.8%, respectively, in those who had five or six segments resected ($P <$ .001).

The influence of a complex hepatic resection on perioperative outcome, stratified by the number of segments resected, is shown in Table 4. When a limited hepatic resection was performed (<3 segments), concomitant additional major procedures increased EBL, LOS, and morbidity but did not affect transfusion requirements or ICU admissions and had no impact on mortality. By contrast, in patients who underwent resection of three or more segments, a complex procedure significantly increased all of these variables (except ICU admission). The most notable finding was a more than twofold increase in operative mortality, from 3% to 6.7% ($P = $ .005).

Table 3. OPERATIVE AND PERIOPERATIVE RESULTS: ALL PATIENTS

A.

Operating time (minutes)	253 ± 2 (median = 240)
Porta hepatis clamp time (minutes)*	31 ± 0.5 (median = 28)
Estimated blood loss (mL)	871 ± 24 (median = 600)
Patients requiring transfusion	880 (49%)
Units transfused	4 ± 0.3 (median = 0)
FFP only	135/880 (15%)
Hospital stay (days)	10 ± 0.2 (median = 8)
Patients requiring ICU admission	112 (6%)

B.

|	
Patients experiencing ≥1 complication	817 (45%)
≥2 complications	345 (19%)
Infections	333/817 (41%)
Mortality	55 (3.1%)
Total complications	1350
Liver/Biliary	369
Perihepatic abscess (110)	
Hepatic insufficiency/failure[1] (99)	
Perihepatic fluid collection (sterile) (97)	
Bile leak/biloma (47)	
Portal vein thrombosis (9)	
Biliary stricture (4)	
Cholangitis (3)	
Pulmonary	344
Pleural effusion (symptomatic) (154)	
Pneumonia (54)	
Atelectasis (45)	
Respiratory insufficiency/failure[2] (43)	
Pneumothorax (32)	
Pulmonary embolus (16)	
Cardiovascular	157
Arrhythmia (83)	
DVT (24)	
CHF (19)	
Angina pectoris/MI (13)	
Cardiac arrest (8)	
Stroke/TIA (7)	
Pericarditis/pericardial effusion (3)	
Genitourinary	136
Urinary tract infection (72)	
Renal insufficiency/failure (41)	
Urinary retention (23)	
Gastrointestinal	109
Ileus (109)	
Bowel obstruction (27)	
Gastrointestinal hemorrhage (21)	
Colitis (16)	
Perforated duodenal ulcer (2)	
Perforated colon (1)	
Miscellaneous	207
Wound infection (94)	
Sepsis/bacteremia (39)	
Unexplained fever (33)	
Perioperative hemorrhage[3] (18)	
Delirium (13)	
Wound dehiscence (10)	
Other[4]	28

* Used intermittently.

[1] Prolonged hyperbilirubinemia unrelated to biliary obstruction or leak, clinically apparent ascites, prolonged coagulopathy requiring FFP, and/or hepatic encephalopathy.

[2] Prolonged ventilatory requirement or reintubation, hypoxia with prolonged supplemental oxygen requirement.

[3] Hemorrhage from operative site.

[4] Line infection (8), hip fracture due to fall (3), hepatic artery pump occlusion (3), decubitus ulcer (2), dehydration requiring readmission (2), syncope (2), air embolus causing cardiac arrest (intraoperative), brachial plexus injury, diaphragm herniation, hypothyroidism, menorrhagia, parotitis, retained drain, splenic injury (requiring splenectomy) (1 each).
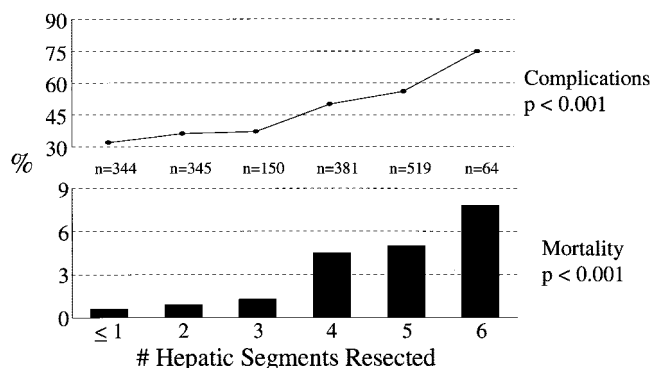
Figure 2. Perioperative complications and mortality stratified by the number of hepatic segments resected.

Factors Associated with Perioperative Morbidity and Mortality

Several preoperative and intraoperative variables were associated with a greater likelihood of perioperative morbidity and mortality on univariate analysis (Table 5). On multivariate analysis, eight independent predictors of morbidity emerged: EBL, number of segments resected, a concomitant major biliary procedure or vascular resection, preoperative hypoalbuminemia or elevated serum creatinine, male gender, and one or more comorbid medical conditions (Table 6). EBL and number of segments resected were also independent predictors of mortality and were the only two common variables in both analyses. Additional factors predictive of mortality were preoperative hyperbilirubinemia or thrombocytopenia, a complex hepatectomy, and age. Patients with extrahepatic biliary malignancy had the highest morbidity and mortality of any other patient group, but neither the primary diagnosis nor the presence of underlying hepatic parenchymal disease was an independent predictor of increased morbidity or mortality.

Trends in Operative and Perioperative Results Over Time

Changes in several operative and perioperative variables over the period of study were analyzed by stratifying pa-tients into five groups based on the date of operation (Table 7). There was a progressive and significant increase in the proportion of segmental resections performed (16% to 33%, $P < .001$), with a corresponding decline in the number of hepatic segments resected (3.5 ± 0.1 to 3.1 ± 0.1, $P = .039$). On the other hand, the proportion of complex hepatectomies increased from 27% to 47% ($P < .001$). The mean EBL decreased by 46% ($P < .001$), with a corresponding decrease in transfusion requirements. The average LOS decreased by over 2 days ($P < .001$), and while the proportion of patients requiring ICU admission and the perioperative morbidity did not change significantly, there was a sharp decline in operative mortality ($P = .01$). In the last 812 consecutive cases (from Jan. 1., 1998, to present), there were 15 perioperative deaths (1.8%) and no deaths in the last 184 cases. Over the study period, there was a small but progressive increase in the proportion of patients with extrahepatic biliary malignancy, but patient demographics and the proportion with comorbid conditions did not vary significantly.

DISCUSSION

In a remarkably short period, hepatic resection has evolved from a high-risk, resource-intensive procedure at the fringe of surgical practice to a mainstream operation with broad indications. Hepatic resection is now firmly established as the most effective treatment for selected patients with primary and secondary hepatobiliary malignancy and the only effective treatment for a number of benign conditions.[3–7,19,20] This evolution is due in large part to improvements in perioperative morbidity and mortality over the past 20 years.

A notable advance has been the increased use of parenchymal-sparing, segmental resections, which has contributed to the improved perioperative results.[3,10,11] This in turn has fostered efforts to expand the indications for hepatic resection and to use it more frequently in combination with other major procedures.[8,9] Several studies have documented better results after hepatic resection for selected indications, but few have specifically evaluated perioperative outcome

Table 4. OPERATIVE AND PERIOPERATIVE RESULTS STRATIFIED BY EXTENT OF OPERATION

	<3 Segments Resected			≥3 Segments Resected		
	Hepatectomy only (n = 468)	Complex hepatectomy (n = 221)	*P* value	Hepatectomy only (n = 667)	Complex hepatectomy (n = 447)	*P* value
EBL (mL)	508 ± 30	653 ± 51	.010	995 ± 42	1,159 ± 59	.019
Patients transfused (%)	31%	34%	.287	55%	66%	<.001
LOS (days)	7.7 ± 0.2	9.1 ± 0.4	<.001	11.1 ± 0.4	12.6 ± 0.4	.006
ICU admission (%)	2.3%	4.5%	.15	6.9%	10%	.074
Morbidity	31%	41%	.016	49%	57%	.007
Mortality	0.9%	0.5%	1.0	3%	6.7%	.005

Table 5. UNIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH PERIOPERATIVE MORBIDITY AND MORTALITY

Variable	Complications	%	P Value	Mortality	%	P Value
Gender						
Male	361/906	39.9	<.001	25/906	2.8	.496
Female	456/897	50.8		30/897	3.3	
Diagnosis						
Benign	59/161	36.7		2/161	1.2	
Extrahepatic biliary cancer	92/142	64.8	<.001	11/142	7.8	.004
Metastatic colorectal cancer	441/1,021	43.2		26/1,021	2.6	
Other	225/479	47		16/479	3.3	
Comorbid conditions						
No	426/1,032	41.3	<.001	22/1,032	2.1	.032
Yes	388/767	50.6		30/767	3.9	
Preoperative albumin						
Subnormal	256/468	54.7	<.001	26/468	5.6	<.001
Normal	542/1,285	42.2		29/1,285	2.3	
Preoperative bilirubin						
Elevated	116/196	59.2	<.001	12/196	6.1	.008
Normal	681/1,557	43.4		42/1,557	2.7	
Preoperative creatinine						
Elevated	59/112	52.7	.118	7/112	6.3	.037
Normal	736/1,635	45		48/1,635	2.9	
Preoperative platelet count						
Subnormal	98/189	51.8	.064	11/189	5.8	.043
Normal	696/1,559	44.6		44/1,559	2.8	
GB/CC/jaundice[1]						
No	700/1,606	43.6	<.001	41/1,606	2.6	.002
Yes	117/197	59.4		14/197	7.1	
≥3 segments resected						
No	234/690	33.9	<.001	5/690	0.7	<.001
Yes	583/1,113	52.4		50/1,113	4.5	
Segmental resection						
No	633/1,277	49.6	<.001	49/1,277	3.8	<.001
Yes	184/526	35		6/526	1.1	
Bilateral resection						
No	406/1,054	38.5	<.001	18/1,054	1.7	<.001
Yes	411/749	54.9		37/749	4.9	
Repeat resection						
No	787/1,718	45.8	.059	53/1,718	3.1	1.000
Yes	30/85	35.3		2/85	2.4	
Complex hepatectomy						
No	470/1,135	41.4	<.001	24/1,135	2.1	.004
Yes	347/668	52		31/668	4.6	
Extrahepatic procedures						
No	570/1,353	42.1	<.001	30/1,353	2.2	<.001
Yes	247/450	54.9		25/450	5.6	
Additional hepatic procedures						
No	696/1,536	45.3	1.000	48/1,536	3.1	.847
Yes	121/267	45.3		7/267	2.6	
Major organ resection						
No	711/1,585	44.9	.310	46/1,585	2.9	.297
Yes	106/218	48.6		9/218	4.1	
Major biliary procedure						
No	700/1,635	42.8	<.001	43/1,635	2.6	.004
Yes	117/168	69.6		12/168	7.1	
Vascular resection						
No	780/1,752	44.5	<.001	46/1,752	2.6	<.001
Yes	37/51	72.6		9/51	17.7	
Transfusion (except albumin)						
No	309/923	33.5	<.001	6/923	0.7	<.001
Yes	508/880	57.7		49/880	5.6	
Liver pathology[2]						
Cirrhosis/steatosis	182/380	47.9	.197	15/380	3.9	.309
Noncirrhotic/nonsteatotic	562/1,275	44.1		36/1,275	2.8	
Liver pathology						
Cirrhosis/fibrosis	80/158	50.6	.153	8/158	5.1	.142
Noncirrhotic/nonfibrotic	664/1,497	44.4		43/1,497	2.9	

* Fisher exact test.
[1] Patients with gallbladder carcinoma, hilar cholangiocarcinoma, or preoperative jaundice.
[2] Cirrhosis and steatosis were not significant when analyzed independently.

Table 5.   Continued

	Complications				
	No		**Yes**		
Variable	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**P Value**
Number of segments resected	986	2.96 ± 1.63	817	3.68 ± 1.59	<.001
Units transfused (except albumin)	986	1.80 ± 5.69	817	6.65 ± 15.1	<.001
Largest tumor size (cm)	986	5.32 ± 4.09	817	6.09 ± 4.92	<.001
Number of tumors	986	2.14 ± 2.39	817	2.31 ± 2.55	.119
Operation time (minutes)	983	238 ± 95	814	271 ± 105	<.001
Blood loss (mL)	954	690 ± 725	797	1088 ± 1246	<.001
Pringle time (minutes)	919	30.8 ± 21.4	760	31.9 ± 20.3	.267
Age (years)	986	57.8 ± 14.3	817	59.6 ± 13.8	.007
Length of stay (days)	986	7.73 ± 2.45	817	13.5 ± 10.6	<.001
Creatinine (mg/dL)	905	0.92 ± 0.25	753	0.99 ± 0.35	<.001
Bilirubin (mg/dL)	912	0.71 ± 1.61	758	1.05 ± 2.49	.001
Platelets (number/μL)	915	254 ± 97	761	267 ± 123	.032
Albumin (g/dL)	920	4.52 ± 9.93	769	4.05 ± 0.56	.188

	Mortality				
	No		**Yes**		
Variable	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**P Value**
Number of segments resected	1,748	3.25 ± 1.65	55	4.40 ± 1.13	<.001
Units transfused (except albumin)	1,748	2.88 ± 7.22	55	39.00 ± 35.30	<.001
Largest tumor size (cm)	1,748	5.61 ± 4.42	55	7.29 ± 5.82	.027†
Number of tumors	1,748	2.21 ± 2.47	55	2.16 ± 2.35	.880
Operation time (minutes)	1,742	252 ± 101	55	286 ± 88	.015
Blood loss (mL)	1,696	822 ± 879	55	2381 ± 2604	<.001
Pringle time (minutes)	1,628	31.4 ± 20.9	51	28.1 ± 22.4	.264
Age (years)	1,748	58.5 ± 14.1	55	62.9 ± 13.1	.021
Creatinine (mg/dL)	1,603	0.95 ± 0.30	55	1.05 ± 0.28	.001
Bilirubin (mg/dL)	1,616	0.81 ± 1.76	54	2.51 ± 6.05	<.001†
Platelets (number/μL)	1,621	261 ± 110	55	239 ± 118	.143
Albumin (g/dL)	1,634	4.32 ± 7.46	55	3.85 ± 0.63	.001†

** Two-sample *t* test.
† Log-transform was used to obtain the *P* value.

and resource utilization within the context of this changing practice.[8] The present study addresses these issues by analyzing a large number of consecutive patients treated in a single center over a short time period.

The data illustrate the importance of resection extent and EBL in determining outcome. Several variables were found to be independent predictors of morbidity and mortality, but only EBL and the number of hepatic segments resected were predictive of both. As the extent of the hepatic resection increased, there was a nearly linear escalation in perioperative morbidity and mortality. Also, a complex hepatectomy was associated with an increased risk of death, while components of this variable, namely a major biliary procedure or a vascular resection, increased the risk of postoperative complications.

The results of the multivariate analysis fit with the trends in perioperative outcome. Over the study period, there was a progressive increase in the proportion of segmental resec-

tions and a decrease in the number of segments resected. Despite these changes, however, 62% of all patients underwent resection of at least three segments. In addition, there was a significant reduction in EBL, which was in part related to the increase in parenchymal-sparing resections. These two factors appear to be primarily responsible for the marked reduction in perioperative mortality, from approximately 4% in the first 5 years to 1.3% in the last 2 years, with no deaths in the last 184 consecutive resections.

The reduction in operative mortality occurred despite a significant increase in the number of complex resections, an observation that initially appears paradoxical. However, the adverse impact of performing additional major procedures was dependent on the number of segments resected. Patients who underwent resection of less than three segments had no increase in transfusion requirements or mortality if a complex procedure was performed, while additional procedures in combination with a major hepatic resection (≥3 seg-

Table 6. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH MORBIDITY AND MORTALITY

Variable	Odds Ratio	95% Confidence Interval	P Value
Morbidity			
Blood loss (L)	1.35	1.18, 1.55	<.001
Number of segments resected	1.20	1.12, 1.29	<.001
Major biliary procedure (yes/no)	2.84	1.92, 4.20	<.001
Preoperative albumin	0.66	0.53, 0.82	<.001
Comorbid (yes/no)	1.40	1.13, 1.74	.002
Gender (M/F)	1.38	1.10, 1.73	.005
Preoperative creatinine	1.78	1.18, 2.69	.006
Vascular resection (yes/no)	2.10	1.04, 4.25	.038
Mortality			
Blood loss (L)	1.692	1.437, 1.994	<.001
Number of segments resected	1.425	1.128, 1.800	.003
Preoperative bilirubin	1.104	1.040, 1.172	.001
Complex hepatectomy (yes/no)	2.181	1.176, 4.047	.013
Preoperative platelet count	0.996	0.993, 0.999	.013
Age	1.030	1.004, 1.056	.025

ments) had a much more profound impact, significantly increasing EBL, transfusion requirements, morbidity, and mortality. The increase in complex resections may explain the greater operating time and stability in ICU admissions and morbidity over the study period. The increase in segment-oriented resections probably also contributed to the longer operating times. Fan et al observed a similar correlation in patients undergoing partial hepatectomy for hepatocellular carcinoma.[3] Segmental resections, although commonly classified as "minor" hepatectomies, are often more demanding technically than classical lobar resections and should not be regarded as simple procedures.

The present study found an increased risk of hepatic resection in the setting of jaundice. Most of these patients had either hilar cholangiocarcinoma or gallbladder carcinoma and required an extended hepatectomy for complete tumor clearance. Morbidity and mortality were higher in these patients than for any other group, in part because of infectious complications associated with preoperative biliary stents.[19,21,22] By contrast, underlying liver disease (cirrhosis, fibrosis, steatosis) did not affect perioperative outcome, probably because of the small number of such patients and the much larger proportion with normal parenchyma in this study. However, preoperative thrombocytopenia, most common in patients with HCC and likely reflecting some degree of portal hypertension, was associated with an increased risk of death.

Belghiti et al recently reported an analysis of 747 hepatic

Table 7. TRENDS IN OPERATIVE AND PERIOPERATIVE RESULTS OVER TIME

	1992–93 (259)	1994–95 (339)	1996–97 (393)	1998–99 (420)	2000–01* (392)	P Value[4]
≥3 segments resected	70%	66%	58%	61%	57%	.004
# segments resected (mean)	3.5 ± 0.1	3.4 ± 0.1	3.2 ± 0.1	3.3 ± 0.1	3.1 ± 0.1	.039
Segmental resections	16%	27%	32%	32%	33%	<.001
Complex hepatectomy	27%	31%	40%	37%	47%	<.001
Blood loss (mL, median)	810	750	600	500	500	<.001
Blood loss (mL, mean)	1180 ± 70	1125 ± 70	878 ± 54	710 ± 44	641 ± 35	<.001
% transfused[1]	57%	49%	47%	47%	47%	.017
# units transfused (mean)	4.1 ± 0.6	5.3 ± 0.8	3.7 ± 0.5	3.9 ± 0.6	3.1 ± 0.4	.009
Operating time (hours, median)	3.8	4.0	4.2	4.1	4.1	<.001
Hospital stay[2] (days, mean)	11.7 ± 0.4	10.9 ± 0.4	10 ± 0.4	10.1 ± 0.5	9.5 ± 0.3	<.001
ICU admission	5%	7.7%	7.6%	5%	5.6%	.54
Morbidity	50%	41%	47%	46%	44%	.67
Mortality	3.5%	4.1%	4.3%	2.4%	1.3%[3]	.01

* To 9/01.
[1] Any blood product except albumin during or after operation.
[2] Date of operation to date of discharge.
[3] No mortalities in last 184 consecutive cases.
[4] Cochran-Armitage test for significance of trends.

resections in the 1990s.[8] A major finding of this study was that a concomitant extrahepatic procedure was the only independent predictor of operative death in patients with no underlying liver disease. The authors observed an increase in the proportion of major hepatic resections and additional major procedures over time but found no significant change in morbidity or mortality. It should be pointed out, however, that the proportion of major resections and additional major procedures was much greater in the present study.

In summary, the present study documents the change in hepatic resectional surgery over the past decade, with more parenchymal-sparing segmental resections and more frequent complex procedures. The number of hepatic segments resected and EBL were the only two predictors of both perioperative morbidity and mortality, and reductions in both appear to be largely responsible for the marked reduction in perioperative mortality. Other factors, such as overall improvement in operative and anesthetic technique and postoperative management, probably also contributed. With respect to utilization of hospital resources, LOS was reduced by over 2 days and the use of blood products decreased significantly, although ICU stay did not change and there was some increase in operating time. The results suggest that complex resections can be performed safely, provided a limited hepatic resection is anticipated; however, caution must be used if a more extensive resection is required, and future studies should be aimed at further clarifying the risk in this group.

Acknowledgments

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DISCUSSION

Dr. David M. Nagorney (Rochester, MN): Dr. Jarnagin and Dr. Blumgart, to succinctly highlight the experience garnered from over 1,800 liver resections is truly impressive. The team effort required to achieve these results is both laudable and noteworthy. You have set the standards which all of us are going to have to match. I have several questions prompted by your talk and your paper.

First, the categorization of wedge resections as segmental may potentially bias the outcome. Some segmental resections or wedge resections are big, but most are very small. Including the wedge to segmental resection could result obviously in segmental sparing and could potentially bias your multisegmental groups if you had multiple small wedge resections. How many of your patients had multiple wedge resections without concomitant anatomical polysegmentectomies? Could this number affect the outcome of your larger group?

Second, your complex resection included both patients with major biliary and major non-biliary resections. Was there a difference in the morbidity and mortality between the major complex biliary and non-biliary resections, and do you recommend staged resections for the non-biliary major resections?

Our studies have shown that steatosis, especially severe steatosis, does affect operative morbidity and mortality. Though not addressed in your

talk, your data did not. How did you measure steatosis? Was it quantitative? And did severity affect outcome?

Finally, one technical question. The anterior segments are easy to excise anatomically because the main segmental portal pedicles are accessible at the hilar or the umbilical plates. Pedicle ligation before parenchymal transection of this group delineates the area to resect and makes an anatomical resection quite clear. The posterior segments 4-A, 7, and 8 are much harder to access. Do you do a hepatotomy to get the pedicle to delineate the resection area or simply get the pedicle after you go through the liver during resection?

PRESENTER DR. LESLIE H. BLUMGART (New York, NY): Dr. Nagorney, thank you very much. There are a lot of questions there, and I will try to answer them in the order they were asked.

We didn't actually categorize wedge resections as segmental. We simply analyzed them within this study as equivalent to one segment so that we could have some reasonable way of analyzing the data. However, I don't believe this caused a shift in the data. Even if all such patients were categorized, the number is small. The figure you asked for, the multiple wedges on their own, were only 43 patients (or 2.4%), and that certainly wouldn't change the results in such a large series.

You suggested that wedge resections carried less risk. I don't think that is really true. In a study that Ron DeMatteo published from our department, there was no difference in mortality and morbidity, blood loss, or length of stay between wedge and segmental resections. What we did find was that for wedge resection, the positive margin rate was 16%, which is in line with Scheele's findings in Germany. This compared to a 2% positive margin rate for anatomical wedge resections.

You are quite right regarding the mortality data. Yes, we had a higher mortality in the presence of vascular resection. It was actually 17%. For biliary-related procedures, in the presence of jaundice, it was 7%. However, that figure is relevant to your second question as to whether we use drainage, since the deaths in that group were nearly all infective and all resulted from the presence of previous drains. So it is very difficult, and I don't know the answer as to whether we should drain these patients before we operate on them or not. As you know, I did a study years ago which suggested that it wasn't necessary. In general we don't do preoperative drainage because I would like to avoid the possibility of biliary infection. But I think that is an unanswered question. At the moment, we don't routinely drain them.

You asked about steatosis. Well, I know you are interested in this and you are conducting a proper study. We have simply relied on the pathology report, and this is a very subjective assessment. However, I am not sure how relevant it is, because we didn't assess liver function other than with Child's-Pugh assessment in cirrhotic patients. Almost all patients that we operated on were Child's A. And there were only 6 of 55 deaths due to liver failure alone. So we are looking at a small problem here. I am not sure that steatosis is that relevant. Perhaps conservation of blood loss is more important, particularly in these patients with soft livers.

As to your final technical point, I don't find posterior sectorectomy much more difficult than anterior sectoral anterior. Yes, it is true, you can get the pedicle easily for the anterior sector. But I think what you meant by hepatotomy was the pedicle ligation technique described by Launois. Yes, we do that if the tumor is far enough away from the pedicle to allow tumor clearance. I have, however, found it increasingly possible to dissect the posterior sectoral vessels extrahepatically and get a very nice line of demarcation. In short, this has not been a major problem.

DR. WILLIAM C. CHAPMAN (Nashville, TN): I would like to thank the American Surgical Association for the privilege of discussing this very important paper, reviewing one of the largest consecutive series of major liver resection from a single institution. This group has been a leader in the field of liver surgery and today has established a new benchmark for hepatic resection, even in the most complex cases. I have several questions for the authors to clarify.

In this series, 18 patients underwent tumor ablation, presumably with cryo- or radiofrequency ablation in combination with liver resection. Given that your data suggest that parenchymal sparing was a significant factor in your improved results over time, should tumor ablation play an even greater role in patients with metastatic and primary liver tumors? I would be interested in your view regarding the recent marked expansion and availability of radiofrequency ablation systems to many centers in the U.S.

Second, what approach do you currently follow for patients with early-stage cirrhosis and small hepatocellular carcinomas who otherwise would receive favorable scoring under the new UNOS MELD-based organ allocation system? While your results suggest that perioperative risks may be reasonable in your hands for standard resection, data from a number of centers suggest that these patients may have better long-term results with liver transplantation.

DR. LESLIE H. BLUMGART (New York, NY): Thank you very much, Dr. Chapman. I don't quite know how to answer your question on RFA ablation. When you said "market expansion," I thought you were going to say "market driven." That is part of the problem. And this is very much an industry-driven technique at the moment. It is not proven. It has a mortality, as recorded in one of the recent papers, of up to 3% in the management of metastatic colorectal cancer, which is not acceptable. It is often used, unfortunately, inappropriately. Everybody in this audience running a specialist hepatobiliary unit knows that we receive patients with large tumors, quite inappropriately treated lying close to major vessels. There is no appropriate study as yet. That is our fault and in our program we haven't yet done a proper comparative study with resection. We are busy setting that up right now aiming to compare RFA with surgical approaches.

We have used RFA mainly for recurrent disease in some cases where resection was inappropriate. We have been using it in irresectable disease in combination with resection and intraarterial infusion pump chemotherapy, and that study is ongoing. So as you see we have made very restricted use of RFA. It probably has a place, but it needs definition. And it should be used in specialist units and not by everybody who can afford a machine.

The other question you asked opens up a Pandora's box. There are serious questions, at least in my mind, as to the suitability of liver transplantation for primary hepatocellular cancer in patients with Child's A liver function. I am particularly concerned about living donors for transplantation for HCC in adults with Child's A liver function.

However, you are quite right, there are some transplant series which suggest that the results of transplantation may be modestly better. On the other hand, there are surgical series which show up to a 65% 5-year survival after resection for small tumors, or indeed after ablative techniques for treatment of small lesions. I don't think that this question is resolved as yet, and further study is needed.

I notice Ronnie Poon and John Wong are in the audience from Hong Kong. I very much liked their study where they actually took a group of such patients (small HCC potentially resectable), resected them, and then reserved transplantation for failure and used that as a way of limiting the need for transplantation. I can't quite remember the figures, but certainly the need for transplantation, selected in that way, was very much less than subjecting all such patients to initial transplantation.